Remarks/Arguments

Claims 1 - 11 remain in this application. Step e of claims 1 and 8, and all remaining claims by virtue of dependency, have been amended replace the prior language; "applying the appropriate rf voltages to the quadrupole ion filter to eject the undesired ions" to the now rewritten "superimposing the appropriate resonant rf frequencies to the quadrupole ion filter to eject the undesired ions." Support for the change may be found at page 15, lines 9-14 and lines 23-26, in the section of the specification where the applicant provides a lengthy discussion of how a quadrupole ion filter may be configured to eject specific ions. No new matter is therefore added by this amendment.

The applicant would note that the changes by this amendment are semantic, rather than substantive, in nature. As explained below, the prior art fails to teach ANY method for "applying the appropriate rf voltages to the quadrupole ion filter to eject the undesired ions." Rather, the prior art, at best, provides a perfunctory discussion of a method for allowing only specific ions to pass through the instrument, which is a different result. However, since this particular step of the present invention is key to the overall method, the applicant felt it better to use the replacement language to describe more precisely how specific ions are ejected from a quadrupole ion filter, and to better distinguish it from prior art methods that accomplish the opposite function; eg. allowing only specific ions to pass through the quadrupole ion filter.

In his office action dated 11/03/2003, the examiner has rejected claims 1, 3, 5 and 7 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al (USP 5,572,022) and further in view of Kirchner et al. (USP 5,464,975). While admitting that Schwartz does not perform the step of "measuring the intensities of the mass spectrum of said first sample", the examiner comments that "it is obvious that they can do such." The examiner then states that because Kirchner et al teach that "by scanning rf voltages to the quadrupole filter, a mass spectrum can be generated to show the signal intensity versus m/z ratio." The examiner concludes that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to measure intensities of a first

sample because this will increase the efficiency of the detection and subsequent analyzing process." The examiner has thus assumed as obvious one of the key distinctions of the pending claims over the prior art, and has failed to account for other distinctions which allow the present invention to achieve significant increases in the dynamic range of a mass spectrometer when compared to the prior art cited by the examiner.

As shown in Schwartz, at column 12, lines 5-30, Schwartz does disclose the ability of the quadrupole to "determine which ions of specific m/e will be stable and pass through to the mass spectrometer." Note that allowing only certain ions to pass through the instrument is NOT the same thing as ejecting only certain ions, as is taught and claimed by the applicant. Indeed, as shown by the prior art and the applicant's disclosure, very different electronic configurations are used for each of these two purposes.

Schwartz's use of a quadrupole in this manner is conventional; many skilled in the art use the quadrupole as a filter to remove all ions except those having a single m/e ratio. Schwartz himself apparently considered the technique sufficiently routine that Schwartz did not bother to describe how quadrupoles are configured to achieve this end. Typically, to accomplish the function described by Schwartz, both rf and dc voltages are applied to the quadrupole, and the frequency of the rf voltage is fixed. The quadrupole works by increasing the voltage of the rf and dc together in a fixed ratio. The Kirchner reference provides an alternate configuration whereby only a rf voltage is applied, again at a fixed frequency, and the voltage is increased to generate the spectrum. In both of these cases only one rf frequency is used, and nowhere do either Schwartz or Kirchner suggest or teach otherwise.

In the case of the present invention, a primary rf frequency, with no dc, is applied to the quadrupole with a voltage that determines the range of ions trapped. Then additional rf frequencies are added to, multiplexed with, this frequency at small voltage values. These additional rf frequencies provide extra energy to the ions that resonate with these frequencies and will be ejected. It is this technique, described in both a theoretical and

experimental bases in the applicant's disclosure beginning at page 9, line 9 through page 16 line 20, that allows the quadrupole to eject on certain m/e species while passing a broad range species of differing m/e ratios through the instrument. Note particularly the discussion at page 10, lines 4-14:

> "During ion excitation in the FTICR cell, a trigger pulse was applied to the 12 bit ADC making it ready for data acquisition. Acquired mass spectra were converted to secular frequency spectra of ion oscillation in the selection quadrupole and a superposition of excitation sine waveforms at the frequencies corresponding to the secular frequencies of the most abundant ion species in the selection quadrupole was synthesized with the ICR-2LS software available at the Pacific Northwest National Laboratory. These excitation waveforms were generated by a 32K plug-in PC DAC board (National Instruments, Austin, TX) and then applied to the selection quadrupole rods *as an auxiliary rf-field.* Using this approach, one or several of the most abundant ion species were ejected from the selection quadrupole resulting in external ion accumulation of lower abundant species for extended periods." (emphasis added)

In contrast, when used in the manner described by Schwartz and Kirchner, the quadrupole only allows ions of a predetermined m/e to pass. As stated by Schwartz, and as is common in the art, when configured in the manner suggested by Schwartz, only a single "notch" of m/e ions are allowed through the quadrupole per scan. All other ions are removed. If a user desires to analyze a variety of ions of different m/e ratios, the rf frequencies applied to the quadrupole must be adjusted sequentially for each specific m/e ratio, and successive scans for each specific m/e ratio must be conducted. While practitioners using the prior art methods have attempted to capture successive scans of a quadrupole downstream in an ion trap, in practice this has proven difficult. Even if trapping successive scans were to prove successful at some point in the future, it will still require a series of successive scans to successfully analyze ions across a wide range of m/e ratios.

The present invention thus differs from prior art methods such as Schwartz and Kirchner because the applicants have made the key insight that in addition to being able to pass ions having only a specified m/e ratio, if additional rf frequencies are superimposed on the quadrupole, the instrument can be used to eject ions of a specific m/e ratio. Further, the applicants have provided a detailed description of how to calculate the specific rf frequencies to be superimposed for any m/e ion that the user wishes to eject. Notably, Schwartz does not recognize this possibility, as Schwartz only discusses the conventional configuration of the quadrupole to select a specific m/e ratio for passing through the instrument (as opposed to ejecting them out of the instrument).

The significance of the capability to eject ions of a specific m/e ratio, (as opposed to the capability of ejecting all ions not of a specific m/e ratio) is not, however, immediately obvious. Only when combined with the inventor's other key insights does this capability achieve a practical purpose.

When specific ions of one or more m/e ratios are ejected, as is required in step e of claims 1 and 8 (and all remaining claims by virtue of dependency) a broad spectrum of ions are allowed to pass in a single scan. Schwartz and Kirchner simply do not recognize this possibility, as Schwarz and Kirchner do not recognize that in addition to using the quadrupole to pass ions of a specific m/e ratio, the quadrupole may also be used to eject ions of a specific m/e ratio. Thus, Schwartz and Kirchner are never confronted with the final piece of the puzzle; selecting the ions that are to be ejected.

The present invention selects which ions are to be ejected by "measur(ing) the intensities of the first sample." Using the information gained in this measurement, the present invention then superimposes additional rf voltages to remove only a specific subset of ions. In this manner, the instrument's dynamic range is vastly enhanced, as ions having a broad range of m/e ratios are allowed to pass on a single scan, while at the same time, large quantities of ions that are not of interest are removed from the quadrupole and never

introduced into the trap. This is not shown or suggested by either Schwarz or Kirchner. Even if Schwartz or Kirchner were to identify ions for subsequent ejection, they do not teach or suggest any method to do the ejection. Thus, the use of the information gleaned from the measurement of an m/z ratio of a first scan to identify specific ions for ejection in a second scan, (or in successive scans), distinguishes the present invention from Schwartz and Kirchner because they have no way to use such information. Only the possession of a method whereby these identified ions may then be ejected allows the instrument to "focus in" on specific ions of interest identified within the sample.

Perhaps the distinction is best illustrated by an example. Consider a typical problem confronting practitioners of mass spectrometry; the identification of proteins. In a typical sample to be analyzed, a number of ions having a broad range of m/e ratios are present. Typically, one or more of these ions will have a high abundance, and many more will be present only in trace quantities. On the first scan of the instrument, those having a large abundance will take up most of the space in the trap. Those of a relatively trace abundance will either not be present at all, or if present, only in very small quantities. When viewing the mass spectrum, a large peak will be observed for those ions having a large abundance. A small peak, or perhaps no peak at all, will be observed for those ions having a relatively small abundance. In the case where the ions are of relatively small abundance are the ions of interest, the practitioner may not be able to detect them. Admittedly, using the technique taught by Schwartz, a practitioner may eventually find these trace ions. By successively tuning the quadrupole across each segment of the entire range of m/e ratios, and conducting separate and sequential scans of each segment, the practitioner will eventually isolate the ion of interest, assuming they are present in each portion of the samples used for successive scans of the instrument. Alternatively, the practitioner may simply get lucky, and "guess" the specific segment of the m/e spectra that contains the ions of interest.

The present invention removes the uncertainty, tedium, time, expense, and guesswork of the each of these possibilities. In the present invention, ions of relatively high abundance

may be immediately removed after the first scan, using the technique of superimposing additional rf frequencies on the quadrupole. While this technique is not taught or suggested in either the Schwartz and Kirchner references, it is described in detail in the applicant's specification. Having removed a specific set of ions, on the second scan, what are trace ions in the sample now comprise the bulk of the ions in the trap. The second scan will thus reveal not a single segment of the m/e spectra, but the entire range of the m/e spectra, excepting those specific high abundance ions having the undesired m/e ratios. The second scan will thus have an abundance of trace ions, each of which are present in quantities sufficient to register a peak that the practitioner can analyze, instead of just a small segment of the spectrum as is disclosed by Schwartz and Kirchner.

The Applicant identified this as the primary point of novelty of the present invention at page 3, columns 16-23 of the specification where the Applicant stated:

> The present invention thus increases the dynamic range of a mass spectrometer by utilizing a quadrupole ion filter as a device to selectively remove one or more undesired ions (peaks), thereby allowing the accumulation and subsequent detection of desired ions in a mass analyzer, such as an ion trap operated as a mass analyzer, adjunct to the ion filter. Typically, but not meant to be limiting, the desired ions are those that are present at relatively low concentrations, while the undesired ions are those that are present at relatively high concentrations. Accordingly, the present invention finds particular utility in instruments where ion capacity is constrained, such as mass spectrometers which utilize ion trapping in their analysis and detection schemes.

The Applicant thus again contests the Examiner's assertion that such would be obvious to one of ordinary skill in the art at the time the invention was made. A plain reading of Schwartz et al. and Kirchner et al., combined with the superior performance detailed in the examples of the present invention contained within the specification, clearly indicates that such was not obvious.

Notably, Schwartz et al. was concerned with the same goals addressed by the present invention. At column 5, lines 27-30, Schwartz et al. state that "the improved performance (of the mass analyzing system) includes *increased dynamic range*, increased sensitivity, improved lower detection limit (sic), and reduction of space charge effects." However, Schwartz et al. as detailed above, Schwartz lacks any method for removing unwanted ions (step e of claims 1 and 8), and thus has no incentive to identify them (step c of claims 1 and 8).

When compared to one and another, the method of the present invention clearly achieves significant improvements in dynamic range over and above the Schwartz et al. method. The present invention describes the improvements in the paragraphs beginning at page 8, line 6 and ending at page 18, line 14. Notably, the method of the present invention was compared directly to a method directly analogous to the Schwartz et al. method. At page 16, lines 2 through 5, the Applicant described the experiments thusly:

> The non-selective accumulation mass spectra were obtained using a 0.5 s trapping in the accumulation quadrupole, while the data-dependent selective ejection of the most abundant ion species in the fly-through mode in the selection quadrupole was followed by a longer 1 s external accumulation period."

In other words, two experiments were run. In one experiment, the trapping time was set to 0.5 seconds in a manner analogous to Schwartz et al. In the second experiment, a longer, 1 second accumulation time was attainable since unwanted ions identified in a first scan were being eliminated. The result of this strategy is given at page 17, line 28 through page 18 line 3, which states:

> "It was found that the number of peptides detected with the alternating sequences (30,771 unique mass classes were identified with the overlap subtracted) was greater by about 35% than that acquired using the non-selective ion accumulation (where 22,664 unique mass classes were identified). The same methodology was subsequently applied with data-dependent selective ion ejection of the two and three most abundant ion species. A 40% increase in the number of unique mass

> classes was achieved when combining the non-selective ion accumulation with data-dependent selective ion ejection of the three most abundant ion species."

In other words, the method of the present invention produced an increased dynamic range that allowed the identification of 35-40% more mass classes when compared with the Schwartz et al. method. Thus, Schwartz et al. and Kirchner et al. cannot possibly provide a basis for a prima facie case of obviousness under 35 USC 103(a) because neither Kirchner et al. nor Schwartz et al. teach or suggest the steps of "identifying undesired ions within said first sample for ejection" or "superimposing the appropriate resonant rf frequencies to the quadrupole ion filter to eject the undesired ions" as required by steps c and e of independent claims 1 and 8, and all remaining claims by virtue of dependency. Such a teaching or suggestion is required for the Examiner to set forth a prima facie case of obviousness. As stated by the Board of Patent Appeals and Interferences, "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Given the demonstrated improvement in the dynamic range of the mass spectrometer when compared to the method taught by Schwartz et al., no "convincing line of reasoning" is possible. As stated by the Federal Circuit, "when differences that may appear technologically minor nonetheless have a practical impact, particularly in a crowded field, the decision-maker must consider the obviousness of the new structure in this light. Such objective indicia as commercial success, or filling an existing need, illuminate the technological and commercial environment of the inventor, and aid in understanding the state of the art at the time the invention was made." Continental Can co. USA v. Monsanto Co., 948 F.2d 1264, 20 USPQ 2d 1746, 1752 (Fed. Cir. 1991).

Plainly, Schwartz et al. were attempting to achieve precisely the same increase in dynamic range as is achieved by the present invention. Equally plain is the fact that the present invention achieved a far greater increase than is possible using the Schwartz et al.

method alone. Accordingly, even if the Examiner maintains the conclusion that the combination claimed by the Applicant's claims 1 and 8 is obvious, the improved dynamic range demonstrated by the Applicant would render the claimed invention unobvious. Again, as stated by the Federal Circuit:

> Evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision-maker remains in doubt after reviewing the art. Stratoflex, Inc. v Aeroquip Corp., 713 F.2d 1530, 1538-40, 218 USPQ 871, 879 (Fed. Cir. 1983).

Accordingly, the Applicant respectfully requests that the Examiner remove his rejection of claims 1, 3, 5 and 7 based on the combination of Schwartz et al. and Kirchner et al.

The Examiner has rejected claims 2, 4, 6, 8, 10 and 11 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al (USP 5,572,022) in view of Kirchner et al. (USP 5,464,975), and further in view of Syage et al. (USP 6,326,615). Regarding claims 2 and 8, the Examiner notes that Syage et al. teaches the interposition of an ion trap in between the quadrupole and the mass analyzer. The Examiner then asserts that the use of a filter is "known in the art." However, the Examiner does not contend, nor does Syage et al. teach, the use of the filter to selectively remove ions identified as undesired in a first sample.

As with the analysis of Schwartz et al. and Kirchner et al. above, this limitation is fundamental to the present invention. With respect to the limitations of "identifying undesired ions within said first sample for ejection" and "superimposing the appropriate resonant rf frequencies to the quadrupole ion filter to eject the undesired ions" contained in claim 8, and claim 2 by virtue of dependency, Syage et al. does not enhance the teachings of Schwartz et al. and Kirchner et al. at all. The examiner admits as much in his statement "While they do not teach the use of a filter, this teaching can easily be

extended to include such because the use of a filter for increased ion passing and measuring is known in the art as applied above..." Thus, any combination of Schwartz et al., Kirchner et al., and Syage et al. is also insufficient to form the basis of a prima facie case of obviousness.

Regarding claims 4, 6, 9, 10 and 11, the Examiner returns to the teaching of Schwartz et al. and asserts that "it is known in the art of sample detection that numerous samples can be detected in a similar fashion, and that rf voltages can be generated by quadrupolar excitation to electrodes of an ion trap, quadrupole filter, or other suitable device as taught by Schwartz et al." While the Examiner's observation is at least relevant to the additional limitations of claims 4, 6, 9 and 10, it does not address the further limitation contained in each of these claims by virtue of their dependency on claims 1 and 8 that the identification of undesired ions forms the basis for the selection of the specific rf voltages that are applied, regardless of the device used. Accordingly, Schwartz still fails to provide the basis for a prima facie case of obviousness under 25 USC 103(a) with respect to claims 4, 6, 9, and 10.

With respect to claim 11, the Examiner has again not addressed the limitation that "steps a-h are repeated to detect further undesired ions for ejection." This omission is telling, since this particular dependent claim isolates and amplifies the core novelty of the present invention. By repeatedly and successively selecting more and more undesired ions for removal over the course of several passes, the method of the present invention allows the operation of the instrument in a manner wherein the user is able to "hone in" on the desired ions by successively eliminating undesired ions that take up valuable space within the ion trap. In this manner the already remarkable enhancements to the mass spectrometer's dynamic range are further enhanced, and the ability to accurately detect progressively smaller concentrations of desired ions within a given sample is created. Neither Schwartz et al, Kirchner et al., Syage et al., or the Examiner's contentions about what is "known in the art" ever address this capability, or the steps taken to achieve this capability as they are set forth in the limitations of claims 1, 8, and 11. Accordingly, the

Examiner's failure to specifically address claim 11 can be interpreted as an admission that the Examiner realizes that none of the prior art teach or suggest these critical aspects of the method of the present invention.

The Applicant therefore respectfully requests that the Examiner remove his rejection of claims 2, 4, 6, 8, 10 and 11 under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al (USP 5,572,022) in view of Kirchner et al. (USP 5,464,975), and further in view of Syage et al. (USP 6,326,615).

Applicant has made an earnest attempt to place the above referenced application in condition for allowance and action toward that end is respectfully requested. If the not allowed, the applicant respectfully requests that the amendments to the claims nevertheless be entered into the record. Should the Examiner have any further observations or comments, she is invited to contact the undersigned for resolution.

Respectfully submitted,

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JAN 19, 2004
Date